# Clinical trial results:
# The effect of Lixisenatide on triacylglycerol and glucose metabolism in patients with type 2 diabetes

## Summary

| | |
|---|---|
| EudraCT number | 2013-002826-22 |
| Trial protocol | GB |
| Global end of trial date | 18 January 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 19 April 2017 |
| First version publication date | 19 April 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CRC333/LIXISL06684 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02049034 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Sanofi identifier: LIXISL06684 |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | University of Surrey |
| Sponsor organisation address | Daphne Jackson Rd, Manor Park, Guildford, United Kingdom, GU2 7WG |
| Public contact | Gill Fairbairn, University of Surrey, ++44 1483 686434, g.fairbairn@surrey.ac.uk |
| Scientific contact | Professor Margot Umpleby, University of Surrey, ++44 1483 686434, m.umpleby@surrey.ac.uk |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 01 March 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The total rate of glucose appearance following the breakfast meal at visits 3 and 7, measured as AUC (0-180 minutes) and AUC (0-240 minutes) where the meal is given at 0 minutes.

Protection of trial subjects:

This was not an efficacy study. All safety assessments were standard.
During the study, adverse events were collected and documented at every visit, regardless of relationship to study medication. These events were coded using the MedDRA (Medical Dictionary for Regulatory Activities) dictionary version 18.1 September 2015 by blinded Surrey CRC data management personnel and checked by the study physician.
The following criteria were used to identify adverse events:
Any unfavourable or unintended sign or symptom
Any deterioration in laboratory data, vital signs or found on physical examination.
All concomitant medications taken during the study were recorded.

Background therapy:

Allowable concomitant diabetes therapy: Metformin

Permitted concomitant therapy: statins, antihypertensives.

Evidence for comparator:

The type of control group: As it was a cross-over trial the participants acted as their own controls. The placebo and GLP-1 injections were indistinguishable and were provided in the same pen-format for subcutaneous injection.
Rationale behind design: A randomised double-blind placebo controlled study design was chosen to study the effect of lixisenatide against a placebo treatment where both the participant and the research group were blinded to the order of the treatment received.
Known or potential problems with design or control groups chosen in relation to the study: Using a cross-over trial can mean that a carry-over effect occurs from the first period to the second period of the trial. This was minimised by using a double-blinded approach and by the presence of a four-week washout period between the treatment arms. Statistical analyses were conducted to determine whether a period effect was present. In this eventuality, comparisons between treatments were made solely at data from period one.

| | |
|---|---|
| Actual start date of recruitment | 01 May 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 8 |
| Worldwide total number of subjects | 8 |
| EEA total number of subjects | 8 |

Notes:

| Subjects enrolled per age group | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 8 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited via the Primary Care Research Network South-East (PCRN SE), approached practices within reasonable travelling distance of Guildford to invite them to support this study, from any REC approved registered research data base, advertisements in local papers including Metro and Evening Standard from Feb 2014-Aug 2015.

### Pre-assignment

Screening details:

There were no wash out or pre assignment periods for screening. Interested patients with type 2 diabetes inadequately controlled by metformin were interviewed on the phone to confirm the inclusion criteria, 24 patients were invited to screening. 14 patients failed to meet inclusion (HbA1c, smoking and weight) and 2 patients withdrew consent.

### Period 1

| | |
|---|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

This is a double blind crossover study. Subjects will be randomised into 2 groups. One group will receive a once daily subcutaneous injection of lixisenatide for 4 weeks followed by a 4 week washout then once daily subcutaneous injection of placebo for 4 weeks. The other group will receive a once daily subcutaneous placebo injection for 4 weeks followed by a 4 week washout then once daily subcutaneous injection of lixisenatide for 4 week. The placebo and GLP-1 injection were indistinguishable

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Placebo |

Arm description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.
Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | PL1 |
| Other name | |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

| | |
|---|---|
| **Arm title** | lixisenatide |

Arm description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly. Identity of investigational products(s) Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide

purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days. Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | lixisenatide |
| Investigational medicinal product code | 320367-13-3 |
| Other name | GLP-1 agonist, Lyxumia |
| Pharmaceutical forms | Suspension for injection in pre-filled pen |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg
lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.

| **Number of subjects in period 1** | Placebo | lixisenatide |
|---|---|---|
| Started | 8 | 8 |
| Completed | 8 | 8 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | overall trial |

Reporting group description: -

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 8 | 8 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Adults (40 - 65 years) | 8 | 8 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 57.3 | | |
| standard deviation | ± 5.26 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 0 | 0 | |
| Male | 8 | 8 | |
| Body mass index | | | |
| Body mass index measured at baseline | | | |
| Units: Subjects | | | |
| 27 - 40 kg/m2 | 8 | 8 | |
| Weight | | | |
| Body weight at baseline | | | |
| Units: Subjects | | | |
| Weight | 8 | 8 | |
| FFM | | | |
| Fat Free Mass at baseline | | | |
| Units: Subjects | | | |
| FFM | 8 | 8 | |
| Creatinine | | | |
| Plasma Creatinine | | | |
| Units: Subjects | | | |
| 64-104 umol/L | 8 | 8 | |
| Fasting glucose<br>Units: Subjects | | | |
| 4.1-6.0 mmol/L | 8 | 8 | |

| | | | |
|---|---|---|---|
| Amylase<br>Units: Subjects | | | |
| less than 118 U/L | 8 | 8 | |
| ALT | | | |
| Alanine transaminase | | | |
| Units: Subjects | | | |
| less than 50 IU/L | 8 | 8 | |
| Total Cholesterol<br>Units: Subjects | | | |
| less than 4 mmol/L | 8 | 8 | |
| Plasma TAG | | | |
| Plasma triacylglycerol | | | |
| Units: Subjects | | | |
| P-TAG | 8 | 8 | |
| HbA1c | | | |
| Haemoglobin A1c | | | |
| Units: Subjects | | | |
| HbA1C | 8 | 8 | |
| lipase<br>Units: Subjects | | | |
| Lipase (5-65 U/L) | 8 | 8 | |
| Calcitonin<br>Units: Subjects | | | |
| Calcitonin (less than 11.8 ng/ml) | 8 | 8 | |
| Body mass index | | | |
| Body mass index at baseline- lixisenatide arm | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 30.3 | | |
| standard deviation | ± 2.9 | - | |
| Body weight | | | |
| body weight at baseline | | | |
| Units: kg | | | |
| arithmetic mean | 93.1 | | |
| standard deviation | ± 9.8 | - | |
| FFM | | | |
| Fat free mass at baseline | | | |
| Units: kg | | | |
| arithmetic mean | 66.5 | | |
| standard deviation | ± 6.5 | - | |
| Creatinine<br>Units: mcmol/L | | | |
| arithmetic mean | 76.6 | | |
| standard deviation | ± 11.9 | - | |
| Fasting glucose<br>Units: mmol/L | | | |
| arithmetic mean | 8.4 | | |
| standard deviation | ± 1.5 | - | |
| Amylase | | | |
| Enzyme | | | |
| Units: U/L | | | |
| arithmetic mean | 44.9 | | |

| | | | |
|---|---|---|---|
| standard deviation | ± 15.3 | - | |
| ALT | | | |
| Alanine Transaminase | | | |
| Units: IU/L | | | |
| arithmetic mean | 42.8 | | |
| standard deviation | ± 18.6 | - | |
| Total Cholesterol | | | |
| Units: mmol/L | | | |
| arithmetic mean | 3.8 | | |
| standard deviation | ± 0.7 | - | |
| Plasma TAG | | | |
| Plasma Triglyceride | | | |
| Units: mmol/L | | | |
| arithmetic mean | 1.76 | | |
| standard deviation | ± 0.78 | - | |
| HbA1C | | | |
| Haemoglobin A1C | | | |
| Units: mmol/mol | | | |
| arithmetic mean | 66.5 | | |
| standard deviation | ± 7.2 | - | |
| Lipase | | | |
| Units: U/L | | | |
| arithmetic mean | 34.5 | | |
| standard deviation | ± 7.7 | - | |
| Calcitonin | | | |
| Units: ng/L | | | |
| arithmetic mean | 3.4 | | |
| standard deviation | ± 1.5 | - | |

## End points

### End points reporting groups

| Reporting group title | Placebo |
|---|---|

Reporting group description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly.
Identity of investigational products(s)
Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.
Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

| Reporting group title | lixisenatide |
|---|---|

Reporting group description:

Lixisenatide and placebo are considered as investigational medicinal product (IMP). Metformin is not considered an investigational product but is an allowed antidiabetic medication to be taken concomitantly. Identity of investigational products(s) Lixisenatide was supplied as disposable pre-filled pen-injectors for subcutaneous injection: 10mcg lixisenatide green pens; 20 mcg lixisenatide purple pens. Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days. Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

### Primary: Area under curve the total rate of glucose appearance; AUC total glu Ra 0-180 min

| End point title | Area under curve the total rate of glucose appearance; AUC total glu Ra 0-180 min |
|---|---|

End point description:

Area under the curve (AUC) for glucose concentration (mmol/L*min) for periods 0-180min, 0-240min and for the whole response curve (0-360min) after a mixed meal at 0 min, at the end of 4 weeks treatment with either lixisenatide or placebo (visits V3 or V7, depending on the randomisation). Lixisenatide/placebo injection was self-administered at -30 min. Results are mean ± SEM.

| End point type | Primary |
|---|---|

End point timeframe:

4 week once daily injection of lixisenatide or placebo, blood samples obtained at 4 weeks

| End point values | Placebo | lixisenatide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: mcmol/kg | | | | |
| arithmetic mean (standard error) | 4883 (± 275) | 2866 (± 274) | | |

| Attachments (see zip file) | Total Glucose Ra/Total GluRa_lixi.png |
|---|---|

### Statistical analyses

| Statistical analysis title | Superiority testing |
|---|---|

Statistical analysis description:

This was a double blind cross over study. A general linear mixed model with repeated measures was used employing SAS PROC MIXED, with explanatory variables period and treatment. The variance covariance matrix used for the repeated measure time course measurements was SP(POW). Participant was a random effect.
Significance was accepted at 5% level, without use of multiplicity adjustment.

| | |
|---|---|
| Comparison groups | lixisenatide v Placebo |
| Number of subjects included in analysis | 16 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.002 [2] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 2017.12 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1156.48 |
| upper limit | 2877.77 |
| Variability estimate | Standard error of the mean |

Notes:

[1] - A general linear mixed model with repeated measures was used employing SAS PROC MIXED, with explanatory variables period and treatment. The variance covariance matrix used for the repeated measure time course measurements was SP(POW). Participant was a random effect.
Significance was accepted at 5% level, without use of multiplicity adjustment.
[2] - P-value for the total glucose Ra chart attached were all at p <0.05.

## Primary: Area under curve of the total rate of glucose appearance; AUC total gluRa 0-240 min

| End point title | Area under curve of the total rate of glucose appearance; AUC total gluRa 0-240 min |
|---|---|

End point description:

Area under the curve (AUC) for glucose Rd measurements (µmol/kg) for periods 0-180min, 0-240min and for the whole response curve (0-360min) after a mixed meal at 0 min at the end of 4 weeks treatment with either lixisenatide or placebo (visits V3 or V7, depending on the randomisation). Lixisenatide/placebo injection was self-administered at -30 min. Results are mean ± SEM.

| End point type | Primary |
|---|---|

End point timeframe:

4 week once daily injection of lixisenatide or placebo, blood samples obtained at 4 weeks

| End point values | Placebo | lixisenatide | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 8 | | |
| Units: mcmol/kg | | | | |
| arithmetic mean (standard error) | 5371 (± 265) | 3979 (± 227) | | |

## Statistical analyses

| **Statistical analysis title** | Superiority testing |
|---|---|

Statistical analysis description:

The study was a double blind crossover study comparing placebo injection with lixisenatide injection.

| Comparison groups | Placebo v lixisenatide |
|---|---|
| Number of subjects included in analysis | 16 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.002 [4] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 1391.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 615.23 |
| upper limit | 2168.52 |
| Variability estimate | Standard error of the mean |

Notes:

[3] - The study was a double blind crossover study comparing placebo injection with lixisenatide injection. A general linear mixed model with repeated measures was used employing SAS PROC MIXED, with explanatory variables period and treatment. The variance covariance matrix used for the repeated measure time course measurements was SP(POW). Participant was a random effect.
Significance was accepted at 5% level, without use of multiplicity adjustment.
[4] - Significance was accepted at 5% level, without use of multiplicity adjustment.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

This includes events from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol.

Adverse event reporting additional description:

The following criteria were used to identify adverse events: Any unfavourable or unintended sign or symptom, Any deterioration in laboratory data, vital signs or found on physical examination.
All concomitant medications taken during the study were recorded

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 18.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

The study was a double blind crossover study comparing placebo injection with lixisenatide injection. Placebo for lixisenatide was supplied as green and purple coloured disposable pen-injectors containing 3 mL of a sterile aqueous solution.

| | |
|---|---|
| Reporting group title | lixisenatide |

Reporting group description:

The study was a double blind crossover study comparing placebo injection with lixisenatide injection. 4 week once daily injection of lixisenatide: Dose titration-10mcg lixisenatide for 14 days, 20 mcg for 14 days.

| Serious adverse events | Placebo | lixisenatide | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 8 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | lixisenatide | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 8 (87.50%) | 5 / 8 (62.50%) | |
| Surgical and medical procedures | | | |
| Tooth extraction | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 8 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nervous system disorders | | | |

| | | | |
|---|---|---|---|
| Diabetic neuropathy | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Belpharitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 8 (25.00%) | |
| occurrences (all) | 2 | 2 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Spigelian hernia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Oral herpes | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 8 (12.50%) | |
| occurrences (all) | 0 | 1 | |
| Tooth abscess | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 8 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 14 April 2014 | Protocol V5, 21/08/2013 with 3 appendices approval date: 14/04/2014<br>Reason for amendment: To improve recruitment of participants.<br><br>Patients will be recruited via the Primary Care Research Network South East (PCRN SE), who will approach practices within reasonable travelling distance of Guildford to invite them to support this study. Suitable patients will be contacted by letter and those that are interested will be contacted by phone to ensure they fulfil the inclusion/exclusion criteria. They will then be sent further information about the study. In addition to this we will contact University of Surrey staff by email, indicating our criteria and inviting them to contact us if they are interested in taking part, then sending them the written information sheet (PIS) and then we will contact them again after a 2-3 days to see if they want to arrange a screening visit. Additionally also by letter from the REC approved registered research database (for example Diabetes Alliance for Research in England; DARE) coordinators inviting them to take part in the study and phone the team for more information or reply by return of the enclosed return slip in the letter (in the envelope provided) giving their permission to be contacted by the research team. The cover letter from DARE team is enclosed. |
| 16 May 2014 | Protocol V5, 21/08/2013 with 4 appendices approval date 16/05/2014<br>1- To improve recruitment of participants.<br>2- The current inclusion criteria of HbA1c and BMI are narrow making recruitment very difficult such that we have not been able to recruit any patients to date into the trial. Widening these criteria will improve recruitment without affecting the integrity of study.<br>Criteria changed from:<br>HbA1c 7.5-8.5% (inclusive),<br>BMI 30-35 kg/m2 (inclusive),<br>to:<br>HbA1c 7.5-9.5% (inclusive)<br>BMI 29-38 kg/m2 (inclusive), |
| 19 August 2014 | Protocol V5, 21/08/2013 with 5 appendices approval date: 19/08/2014<br>To improve recruitment of participants.<br><br>Protocol V5, section on participant recruitment was amended as follows: We will advertise the study in local papers including Metro and Evening Standard on paper as well as digitally available App for the above newspapers. Please refer to appendices 2, 4 & 5.<br><br>Protocol V5, Selection of patients, exclusion criteria, page 13:<br>Patients on beta blockers are now included in inclusion criteria. |

| | |
|---|---|
| 09 March 2015 | Protocol V5, 21/08/2013 with 6 appendices approval date: 09/03/2015<br>To verify the stable diabetes control-<br>We added an HbA1c measurement to visit 1 - in order to have up-to-date reassurance of the stability of HbA1c at the start of the study. To provide further reassurance, we will ensure that the metformin dose is unchanged since their last GP visit and so will enter the statement "no changes to metformin dose since that last GP surgery check up".<br>To improve recruitment of participants-<br>The current inclusion criteria of BMI (29-38 kg/m2) are narrow, making recruitment very difficult. Widening these criteria will improve recruitment without affecting the integrity of the study.<br>Amendment to expenses claim-<br>We have found that eight visits, of which four are over seven hours in duration, over the course of<br>the three months study, is affecting the recruitment rate from patients who are in employment due to the low remuneration. We believe the increase in compensation payment should increase recruitment numbers from people in employment who often have to take unpaid leave to meet the time commitments of the study. We will pay the extra reimbursement to the patients who have already been on the trial and received their payment at the original rate.<br>Change to personnel- Two personnel, one a replacement student and the other recruitment officer have left the University, so these have been assigned off study with their end dates. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| 1- The timing of the IMP at visit 4 and 8. The IMP, given at -270 min, would have been preferable to be given at 0 time.<br>2- A crossover effect was demonstrated statistically for a number lipid parameters reducing the power of calculation. |

Notes: